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## REMARKS

The prosecution status of the present application is as follows: the rejections under Section 112, first and second paragraphs, have been withdrawn in view of the Amendment and response filed January 3, 2001. The only remaining rejections are under Sections 102 and 103, based on the prior art references cited.

Applicants' amendment and response to the Final Office Action mailed May 9, 2001 was filed November 9, 2001. In the response of November 9, 2001, Applicants submitted new claims 38-45, which were the same as previously pending claims except for numbering and dependency. Claims 1-26 and 34-37 have been canceled without prejudice. In order to compare the currently pending claims with those referenced in previous office actions and responses, the renumbered claims correspond as follows:

- Claim 38 is as filed claim 17, amended as described herein
- Claim 39 is as filed claim 5
- Claim 40 is as filed claim 7
- Claim 41 is as filed claim 8, amended as described herein
- Claim 42 is as filed claim 9
- Claim 43 is as filed claim 13
- Claim 44 is as filed claim 14
- Claim 45 is as filed claim 15.

None of the amendments made herein constitutes the addition of new matter.

The claims as amended recite a method for prophylaxis or treatment of a *Plasmodium* infection by inhalation of a NO-modifying agent. Support and definition of "NO-modifying agent" is provided in an extensive passage of the Specification, page 3, line 13 to page 4, line 16.

Administration of an NO-modifying agent by inhalation is described at several places in the Specification, including page 6, lines 3-6 and 14-20, page 7, lines 14-15, page 16, lines 24-27, page 17, line 12, and page 18, lines 5-9. In particular, the passage at page 16, lines 24-27, describes treatment of *Plasmodium* by inhalation of NO, NO-inducing cytokine, R-NO or R'-S-NO, all as described in the Specification.

Claim Rejections under 35 U.S.C. 102:

Claims 1-6, 9-13, 15, 17-19, 22-23, 26, and 34-37 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Seguin et al. Applicants respectfully traverse this rejection as applied to the current claims.

The Seguin et al. reference does not anticipate the claimed invention. This reference describes an experimental system in which mice were first immunized by exposure to mosquitos infected with irradiated *Plasmodium berghei* which protected the mice against subsequent viable sporozoite challenge. To gain insight into how this protection might occur, a nitric oxide synthase (NOS) inhibitor was administered to the animals by gastric instillation during the challenge step. Based on these experiments, it was concluded that the induction of endogenous NOS enzyme might contribute to the protection against malaria in the immunized animals.

In contrast, the claimed invention is a method of preventing or treating malarial infection by inhalation of an exogenous NO modifying agent in human patients. This invention is based on the inventor's finding that NO production retards parasitic growth and increased levels of NO prevent disease development in non-immunized human patients.

Thus, the distinctions between Seguin et al. and the claimed invention are readily apparent. Seguin et al. does not anticipate the claimed invention because it does not disclose all aspects of the invention as currently claimed, in particular the administration of an NO-modifying agent by inhalation. The subject matter of Seguin et al. (*Plasmodium*-immunized mice) is not the subject of the current claims. The rejection under 35 U.S.C. 102 can be withdrawn.

Seguin et al. is also cited in support of obviousness of claims 8, 14, and 16. This reference cannot provide any suggestion or motivation to make the claimed invention. As is stated therein, "As to whether human hepatocytes exhibit antimalaria activity when stimulated to produce NO, remains to be examined." (See page 353, bottom of the left column). Further, the results obtained from immunized mice of Seguin et al. would not suggest the method of preventing or treating malarial infection in humans by inhalation of an exogenous NO modifying agent.

Claim Rejections under 35 U.S.C. 103:

Claims 1-7, 9-13, 15, 17-26 and 34-37 are rejected under 35 U.S.C. 103 (a) as allegedly unpatentable over Kremsner et al. in view of Liew et al. Applicants respectfully traverse this rejection as applied to the current claims.

Kremsner et al. reports a correlation between endogenous NO levels and severity of the disease in human patients. However, it is not clear from Kremsner et al. whether the NO production is the symptom of the disease pathology or a component of the body's defense mechanism. Thus, it is confusing as to whether high NO levels are beneficial or harmful to the patients.

Liew et al. describes the studies involving *Leishmania major*. There is no mention or suggestion of parasites which cause malaria.

Based on the confusing reports of Kremsner and the results on *Leishmania major* by Liew et al, one skilled in the art cannot make the claimed invention. Withdrawal of the rejection as applied to the current claims under 35 U.S.C. (103) is respectfully requested.

Claims 8, 14, and 16 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Seguin et al. or Liew et al. in view of Stamler et al. Applicants respectfully traverse this rejection.

The shortcomings of Seguin et al. has been pointed out above. Liew et al. is not relevant to claims limited to *Plasmodium* infection. Stamler et al. does not provide teachings or suggestions that bridge the gap between Seguin et al. and the invention as currently claimed. The reference merely describes an analytical method to determine plasma levels of free nitric oxide and S-nitrothiols. Such a method might be a useful adjunct for monitoring treatment by the method of the invention, but fails to suggest treatment by inhalation of an NO modifying agent. There is no suggestion or motivation in Stamler et al. for a person of ordinary skill to make and use the claimed invention in combination with Seguin et al., since neither reference even hints at a method of treatment by inhalation of an NO modifying agent.

Based on the foregoing, Applicants submit that the rejection under 35 U.S.C. 103 (a) is not justified and withdrawal of the rejection is respectfully requested.

Conclusion

It is believed that the claims as amended are considered to be in condition for allowance. Careful consideration and passage to issuance is respectfully requested.

This Amendment is accompanied by a Request for Continued Examination and a check for \$370.00, as well as a Petition for Extension of Time (four months) and a check for \$720.00. If the amounts submitted are incorrect, please deduct from Deposit Account No. 07-1969 the appropriate fee for this submission and any extension of time required.

Respectfully submitted,



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Attorney docket No.73-97  
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**Marked up version of amended claims in attached Amendment.**

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38. (Once amended) A method for the prophylaxis or treatment of infection by a *Plasmodium* species in a mammal, said method comprising [administered] administering to said mammal by inhalation an NO modifying agent which kills, inhibits or otherwise retards the growth, infectivity or pathogenesis of the *Plasmodium* species.
41. (Once amended) A method according to claim 38 wherein [NO is administered by inhalation to increase systemic NO levels or NO effect] the agent is NO.